

39727



PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of

Capon et al.

Group Art Unit: 1647

Serial No.: 08/238,405

Examiner: Hayes, R.

Filed: 5 May 1994

For: CHIMERIC CHAINS FOR RECEPTOR-
ASSOCIATED SIGNAL
TRANSDUCTION PATHWAYS

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SUBMISSION OF APPELLANTS' BRIEF ON APPEAL

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Submitted herewith please find an original and two copies of Appellants' Brief on Appeal. Please charge the statutory fee of \$160.00 to Deposit Account No. 18-2220. Authorization also is given to charge or credit any difference or overpayment to Deposit Account No. 18-2220. A duplicate copy of this paper is attached.

Respectfully submitted,

A handwritten signature in black ink, appearing to read "Dean H. Nakamura Reg. No. 45,869". Below the signature, the name "Dean H. Nakamura" is printed in a smaller, clean font, followed by "Attorney for Applicants" and "Reg. No. 33,981".

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Dated: 26 March 2002

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APPELLANTS' BRIEF ON APPEAL

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

In accordance with the provisions of 37 C.F.R. § 1.192, Appellants submit the following:

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APPELLANTS' BRIEF ON APPEAL
Serial No.: 08/238,405

TABLE OF CONTENTS

REAL PARTIES IN INTEREST	3
RELATED APPEALS AND INTERFERENCES	4
STATUS OF CLAIMS	5
STATUS OF AMENDMENT	6
SUMMARY OF THE INVENTION	7
ISSUES	8
GROUPING OF CLAIMS	9
ARGUMENTS	10
CONCLUSION	19
APPENDIX	21
APPEALED CLAIMS	21

APPELLANTS' BRIEF ON APPEAL

Serial No.: 08/238,405

I. REAL PARTIES IN INTEREST

The real parties in interest by virtue of Assignment are Cell Genesys, Inc. and The University of California.

APPELLANTS' BRIEF ON APPEAL

Serial No.: 08/238,405

II. RELATED APPEALS AND INTERFERENCES

Interference no. 103887 may be relevant.

APPELLANTS' BRIEF ON APPEAL
Serial No.: 08/238,405

III. STATUS OF CLAIMS

The application was filed with 56 claims.

In the Preliminary Amendment filed 7 August 1995, claims 1-37 and 55-56 were canceled. New claims 79-92 (sic, 57-70) were added.

In the Amendment filed 19 March 1996, claim 70 was canceled.

In the Amendment filed 24 December 1996, claims 38-54 were cancelled. Claim 58 also was canceled.

In the Amendment filed 15 June 1998, claims 60-63, 66 and 68 were canceled. Claim 71 was added.

In the Amendment filed 4 April 2001, claim 71 was canceled.

As noted in the Office Action mailed 27 June 2001, claims 57, 64, 65, 67 and 69 are rejected. Claim 59 is objected to.

APPELLANTS' BRIEF ON APPEAL
Serial No.: 08/238,405

IV. STATUS OF AMENDMENT

As noted in the Advisory Action mailed 18 January 2002, the Amendment After Final filed 2 January 2002 was not entered.

APPELLANTS' BRIEF ON APPEAL
Serial No.: 08/238,405

V. SUMMARY OF THE INVENTION

The invention of interest involves tripartite chimeric molecules that span the membrane of a host cell. The extracellular region is non-MHC restricted and is capable of binding to a specific ligand, page 7, lines 21 and 22. The cytoplasmic region is associated with initiating a signal in a cell, page 7, lines 16-19. Those two regions are joined by a transmembrane domain that spans the membrane, page 7, lines 27 and 28.

The extracellular domain comprises the antigen binding portion of a single chain antibody, page 15, line 9. The single chain antibody can bind to a protein on the surface of a target cell, page 13, lines 5-19, or to viral proteins, page 17, lines 18-29.

Particular cytoplasmic domains of interest are the zeta chain, the eta chain, the gamma chain, the delta chain and the epsilon chain of the T cell receptor, page 7, lines 24-26; the gamma chain of the F_c receptor, page 7, line 26; or a tyrosine kinase, page 7, line 26.

The tripartite molecule is expressed as a cell surface membrane protein, page 20, lines 23-25. On binding ligand, the chimeric molecule of interest initiates a signal in the cell, page 20, lines 25-28. The initiation of a signal by the receptor of interest is confirmed by the observation that the chimeric molecule of interest can induce a signal in the absence of endogenous T cell receptor molecules, page 30-38, and particularly page 30, lines 25-32; page 31, lines 14-18; and page 34, lines 10-18.

APPELLANTS' BRIEF ON APPEAL
Serial No.: 08/238,405

VI. ISSUES

I. Claims 57, 64, 65, 67 and 69 were rejected under 35 U.S.C. § 112, first paragraph for an alleged want of written description as the Examiner stated the specification does not describe in such a way to reasonably convey to one skilled in the relevant art that inventors, at the time the application was filed, had possession of the claimed invention. The Examiner characterized the rejection as one of new matter. The Examiner stated that the specification does not teach the generic concept of transducing a signal in the absence of a T cell receptor.

II. Claims 57, 64, 67 and 69 were rejected under 35 U.S.C. § 102(e) over Eshhar et al.

APPELLANTS' BRIEF ON APPEAL

Serial No.: 08/238,405

VII. GROUPING OF CLAIMS

- I. Claims 57, 64, 65, 67 and 69 stand and fall together.
- II. Claims 57, 64, 67 and 69 stand and fall together.

VIII. ARGUMENTS

Before explaining why the rejections are improper, the claimed invention will be described in detail greater than that presented hereinabove in the Summary.

As noted in the second full paragraph on page 3 of the instant application, it was known that the T cell antigen receptor was a complex of a number of different protein chains.

There is the antigen/MHC binding subunit that is variable and is known as T_i of the T cell receptor. As noted at lines 14 and 15 on page 3 of the instant specification, T_i consists of the α and β heterodimer. Each of the α and β chains resembles immunoglobulin in having a constant domain and a variable domain. The variability of the two chains is related to the diversity of the heterodimer and the ability to bind to a variety of ligands.

Thus, it was known that the α and the β chains of the T cell receptor have the sole function of being presented at the surface of the cell and being responsible for binding ligand.

The other portion of the T cell receptor comprises five invariant chains, zeta, eta, gamma, delta and epsilon. Sometimes, the latter three subunits are known collectively as CD3. As noted at lines 15-20 of the second full paragraph on page 3 of the instant application, the CD3-zeta/eta complex does not bind ligand. It was thought that the CD3-zeta/eta complex underwent alterations as a consequence of the interaction of antigen with the T_i heterodimer.

As provided in the second full paragraph on page 4 of the application, zeta is an alternatively spliced variant of the same gene that produces eta. Thus, the two molecules are almost identical in sequence as well as in function.

APPELLANTS' BRIEF ON APPEAL
Serial No.: 08/238,405

In the paragraph bridging pages 4 and 5, the instant specification teaches that the three CD3 chains are structurally related to each other and were implicated to be involved in signal transduction. Sequences similar to the repeated active motif found in zeta are also present in the cytoplasmic domains of the CD3 chains. Thus, the CD3 chains likely share properties and functions with zeta.

The gamma chain of the F_c receptor is homologous to the zeta chain, first full paragraph on page 4 of the instant application. The gamma chain shares structural features with zeta and it was believed that gamma carries out functions similar to that of zeta.

As noted in the paragraph bridging pages 1 and 2 of the instant specification, when the T cell receptor is activated on binding ligand, a signal is generated in the cell. The change in the cytoplasmic portion in the T cell receptor results in binding to other proteins that are activated and may carry out various functions. One of such molecules is tyrosine kinase as taught in the paragraph bridging pages 5 and 6 of the instant specification. Thus, a tyrosine kinase can be used as the intracellular domain of a receptor of interest.

A key feature of the instant invention is taking those portions of the T cell receptor that comprise the invariant chains, as well as other molecules of similar structure and function, and combining those molecules into a tripartite composite molecule that spans the cell membrane and signals on binding ligand. The molecules that can contribute to the intracellular domain of a chimeric receptor of interest were found to be molecules that initiate a signal. That is distinct from molecules that do not have a signaling function, for example, the α and β chains of the T cell receptor which have only ligand binding activity.

APPELLANTS' BRIEF ON APPEAL
Serial No.: 08/238,405

Thus, a molecule of interest is a transmembrane molecule with an extracellular domain, a transmembrane domain and an intracellular domain. The extracellular domain comprises the antigen-binding portion of a single chain antibody. The transmembrane domain traverses the membrane and connects the extracellular domain with the intracellular domain. The intracellular domain comprises the invariant chains of the T-cell receptor, zeta, eta, gamma, delta and epsilon as well as the gamma chain of the F_c receptor and tyrosine kinase. Those molecules share structure and initiate a signal in the cell.

A feature of the instant chimeric receptors is the ability to signal autonomously. Thus, the chimeric receptors of interest initiate a signal, without, for example, endogenous T cell receptor. That is an inherent feature of a receptor of interest.

To demonstrate that a chimeric receptor of interest can initiate a signal on binding ligand, experiments were conducted in which a DNA construct encoding a chimeric receptor of interest was introduced into two related cells. One cell, the Jurkat cell, expresses T cell receptor. The second cell is a mutant of the first and does not express T cell receptor, paragraph bridging pages 30 and 31 of the instant specification. Thus, the JRT3.T3.5 cell is a mutant Jurkat T cell that does not express T cell receptor.

Nevertheless, when the JRT3.T3.5 cell was transformed and expressed a chimeric receptor of interest, and was stimulated with the appropriate ligand, the chimeric receptor of interest initiated a signal in the mutant JRT3.T3.5 cell that does not express T cell receptor.

Thus, for example, as noted at pages 33-36 of the instant specification, when an antibody directed to the extracellular domain of a receptor of interest was exposed to a cell expressing that chimeric receptor, the cell was triggered and an increase in cytoplasmic free

APPELLANTS' BRIEF ON APPEAL
Serial No.: 08/238,405

calcium was observed. As a negative control, when that same cell was exposed to an antibody directed to T cell receptor, essentially the α and β chains, no detectable increase in intracellular calcium was noted because the JRT3.T3.5 cells does not express T cell receptor.

In another series of experiments using JRT3.T3.5 cells transformed to express a chimeric receptor of interest, the signal initiated caused an increase in inositol phosphates. On the other hand, the transformed T cell receptor deficient cell did not demonstrate a similar increase in inositol phosphates when stimulated with antibody directed to T cell receptor. That is understandable since the JRT3.T3.5 cell does not express T cell receptor and thus cannot be stimulated by antibody to the T cell receptor.

Similarly, stimulation of the chimeric receptor of interest also activated tyrosine kinases to phosphorylate protein substrates, paragraph bridging pages 34 and 35 of the instant specification. Stimulation of the chimeric receptor of interest also led to several late events in T cell activation including expression of the CD69 cell surface molecule as well as production of interleukin-2.

The instant specification teaches how to obtain sequences encoding a single chain antibody, sequences encoding a transmembrane domain and sequences encoding an intracellular domain and combining those in a single transcriptional unit for cloning. The sequence encoding a chimeric receptor of interest is placed in a suitable vector as known in the art and propagated in a suitable cell. Thus, the instant specification provides a thorough teaching, in view of the state of the art, of how to make and how to use a chimeric receptor of interest, commensurate in scope with the claims.

APPELLANTS' BRIEF ON APPEAL
Serial No.: 08/238,405

I. Turning now to the first of the outstanding issues, as noted on page 3 of the Office Action mailed 27 June 2001, claims 57, 64, 65, 67 and 69 were rejected under 35 U.S.C. § 112, first paragraph. The Examiner stated that the rejection is one of new matter. At lines 11-13 on page 3 of the Office Action, the Examiner stated that the concept of transducing a signal in the absence of a T cell receptor is new matter. The Examiner goes on to state that no where in the specification is the generic concept of transducing a signal in the absence of a T cell receptor contemplated for a cytoplasmic domain that does not include the zeta chain of the F_c receptor. The Examiner recommended combining claims 57 and 59.

The rejection is traversed for the following reasons.

First, it is unclear what is meant by the phrase in the Office Action, "zeta of the F_c receptor," because the zeta chain is part of the T cell receptor and not part of the F_c receptor. Moreover, zeta is not recited in claim 59.

Therefore, the invention may have been misunderstood. That misunderstanding of the invention of interest and of the components that comprise a receptor of interest renders the instant rejection as well as the art rejection inapposite.

In any event, the pending claims are patentable. The guiding law on written description, new matter and inherency teaches that it is not whether the specific word or claim is present in the specification as filed, but whether the concept expressed by the word was present. In re Anderson, 47 F.2d 1237, 176 U.S.P.Q. 331 (CCPA 1973). To satisfy the written description requirement, a disclosure does not have to prove in haec verba support for the claimed subject matter so long as one of ordinary skill can recognize that the applicant

APPELLANTS' BRIEF ON APPEAL
Serial No.: 08/238,405

invented what was claimed. Purdue Pharma L.P. v. Faulding Inc., 230 F.3d 1320, 56 U.S.P.Q.2d 1481 (Fed. Cir. 2000). Thus, written description exists if the artisan would know the claimed invention even though every nuance of the claimed invention is not explicitly described in the specification. In re Alton, 76 F.3d 1168, 37 U.S.P.Q.2d 1578 (Fed. Cir. 1996).

Inherent properties that do not constitute new matter are those which would be obvious to one skilled in the art from the very nature of the material. In re Smythe et al. 480 F.2d 1376, 178 U.S.P.Q. 279 (CCPA 1973); Jacobs v. Lawson et al., 214 U.S.P.Q. 907 (BOPI 1982). Physical properties of a compound are inherent properties of a compound. Ex parte Davisson et al., 133 U.S.P.Q. 400 (BOPI 1958). There is no requirement that superior features or advantages of a claimed invention be disclosed in the specification. It is enough if the basic property in which the advantage resides is disclosed. In re Slocombe, 510 F.2d 1398, 184 U.S.P.Q. 740 (CCPA 1975).

As noted hereinabove, the instant specification teaches a structural and functional similarity amongst all of the molecules recited contributing a cytoplasmic domain to a chimeric receptor of interest. The instant application teaches that zeta initiates signals on stimulation of the receptor. The working examples also provide details for constructing other chimeric receptors of interest. Notably, the starting materials, i.e., the gene sequences encoding suitable domains for a chimeric receptor of interest, are known in the art or would be readily available to an artisan.

In further support of the teachings of the instant application, reference is made to Letourneau & Klausner, or record, teaching receptors similar to that claimed, made as taught

APPELLANTS' BRIEF ON APPEAL
Serial No.: 08/238,405

in the instant specification and containing epsilon as the cytoplasmic domain. Eshhar et al., of record, teach chimeric receptors similar to that claimed, made as taught in the instant specification and containing the gamma chain of F_c receptor. Kolanus et al., of record, teach chimeric receptors similar to that claimed, made as taught in the instant specification and containing syk tyrosine kinase as the cytoplasmic domain.

Also, attached hereto are copies of recently issued patents that teach receptors that are similar to that claimed and made as taught in the instant specification. Thus, a chimeric receptor containing CD28 as the cytoplasmic domain is taught in U.S. Pat. No. 5,712,149. A chimeric receptor containing multiple extracellular domains is taught in U.S. Pat. No. 6,103,521. A chimeric receptor comprising a jak tyrosine kinase is described in U.S. Pat. No. 5,837,544. A chimeric receptor comprising a src tyrosine kinase is taught in U.S. Pat. No. 5,504,000. Receptors made with tyrosine kinases by pass the T cell receptor and initiate signal independent of T cell receptor chains.

The Examiner has provided no evidence to even suggest that any of the particular members of molecules that can comprise a cytoplasmic domain would not operate as alleged in the instant application.

Thus, the instant application clearly conveys to the artisan that the chimeric receptors of interest can operate independent of a T cell receptor as signaling molecules. That is an inherent feature of the claimed receptors, as would be evident to the artisan on reading the instant specification.

Accordingly, as explained hereinabove, the rejection is improper. Moreover, as the claimed invention clearly is supported by the instant specification as would be evident to one

APPELLANTS' BRIEF ON APPEAL
Serial No.: 08/238,405

of skill in the art, the requirements of 35 U.S.C. § 112, first paragraph are satisfied. Hence, the rejection must be withdrawn.

II. In item 8 on page 4 of the Office Action mailed 27 June 2001, claims 57, 64, 67 and 69 were rejected under 35 U.S.C. § 102(e) over Eshhar et al. The Examiner stated that arguments relating to Gross et al. were no considered because Gross et al. was never properly made of record. The Examiner also stated that the Eshhar invention is directed to the T cell receptor alpha, beta, gamma and delta chains.

The rejection is traversed for the following reasons.

First, it should be noted that Gross et al. is a reference cited and relied on by the Examiner in the Office Action of 8 September 1998 and thus, is properly of record. Therefore, the Examiner cannot dismiss the arguments of record and he is asked respectfully to review the record regarding explaining the irrelevance of the Gross et al. technology, and hence, Eshhar et al., to the claimed invention.

Second, Goverman et al. and Weiss were provided to demonstrate the state of the art in a reply to an Office Action. Weiss was provided to the Examiner on 8 March 1999 for that purpose and the Examiner did not raise an objection to Weiss in the subsequent Office Action of 26 May 1999. Clearly, then, the Examiner had already considered Weiss for the purpose of chronicling a fact of the state of the art.

Moreover, as noted in MPEP 609 C(3), documents submitted by applicant when replying to an Office Action need not satisfy the requirements of 37 C.F.R. 1.97 and 1.98 to

APPELLANTS' BRIEF ON APPEAL

Serial No.: 08/238,405

be considered. Therefore, the Examiner is requested respectfully to consider the teachings of all of the references submitted to the Patent Office as those reference are probative on the state of the art, and particularly on the distinctions of the instant invention over the references relied on by the Examiner.

The cloning rationale of the Eshhar et al. constructs is a shuffling of constant and variable domains between immunoglobulin and immunoglobulin-like molecules, column 2, fourth full paragraph and particularly, lines 31-35; Figures 8 and 9; column 3, lines 42-46; and column 4, lines 4-8 of Eshhar et al. Molecules of the T cell receptor having an immunoglobulin-like structure include the alpha and beta chains, paragraph bridging columns 1 and 2, and first full paragraph of column 2 of Eshhar et al. As noted in the discussion hereinabove detailing a receptor of the instant invention, it was known in the art that the alpha and beta chains do not signal on their own.

With respect to the gamma and delta chains used by Eshhar et al., as explained in the Amendment of record, the gamma and delta chains of Eshhar et al. are in fact homologues of the alpha and beta chains. The gamma and delta chains of Eshhar et al. are not the same as the CD3 gamma and CD3 delta chains of the instant invention. The art was well aware of that distinction as noted in Weiss of record. The relatedness of alpha and beta, to gamma and delta was reported by Brenner et al. in 1988 (Adv. Immunol. 43:133-1910).

In the context of making the Eshhar et al. receptors, that is consistent because the Eshhar et al. receptor arises from shuffling variable and constant domains. Thus, the gamma and delta chains of Eshhar et al. must be of the immunoglobulin superfamily and have an immunoglobulin-like structure, namely, contain a variable domain and a constant domain.

APPELLANTS' BRIEF ON APPEAL
Serial No.: 08/238,405

That is taught in column 4, lines 7-8 of Eshhar et al. where Eshhar et al. teach the constant region of gamma and delta.

On the other hand, the gamma and delta chains of the instant invention comprise the invariant CD3 complex of T cell receptor are not of the immunoglobulin superfamily. That is to say, the CD3 gamma and CD3 delta chains do not contain a variable region and a constant region as do the gamma and delta chains of Eshhar et al. The non-immunoglobulin-like structure of CD3 gamma and CD3 delta of the instant invention was known, see pages 3-5 of the instant specification.

Therefore, it is clear that because Eshhar et al. is essentially shuffling variable and constant domains between immunoglobulin and immunoglobulin-like molecules such as the alpha, beta, gamma and delta chains of T_I, Eshhar et al. clearly is distinct from the instant invention, which has nothing to do with alpha and beta as well as any other immunoglobulin-like molecules such as gamma and delta for making the cytoplasmic domain of a chimeric receptor of interest.

Finally, the host cells used to express the Eshhar et al. receptor are cells that express T cell receptor. Therefore, the chimeric receptors of Eshhar et al. that comprise the alpha and the beta chains are interacting with endogenous T cell receptor to stimulate a signal. Eshhar et al. teach that the cell expressing the Eshhar et al. receptor is one that expresses the CD3/TcR complex, column 1, lines 17-18; column 3, line 66; and column 9, lines 3-6 of Eshhar et al.

That is distinct from the instant receptors that signal in that absence of T cell receptor.

APPELLANTS' BRIEF ON APPEAL
Serial No.: 08/238,405

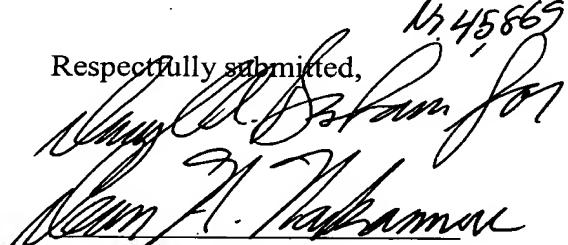
Therefore, on careful consideration of the basic biology of the component molecules used by Eshhar et al. and those claimed in the instant application, it is clear there is no anticipation and the rejection must be removed.

XI. CONCLUSION

The claimed invention is in compliance with 35 U.S.C. 112, and is free of the cited art. Withdrawal of the rejections and early indication of allowance is solicited earnestly.

The instant Brief on Appeal is being filed in triplicate. Appellants hereby petition for any extension of time that may be required to maintain the pendency of the instant application, and any required fee for such extension is to be charged to Deposit Account No. 18-2220.

Respectfully submitted,



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Dated: 26 March 2002

APPELLANTS' BRIEF ON APPEAL
Serial No.: 08/238,405

APPENDIX

57. A chimeric protein comprising in the N-terminal to C-terminal direction:
an extracellular antigen-binding domain of a single chain antibody that binds
specifically to an antigen, wherein said antigen is a protein on the surface of a cell or a viral
protein;
a transmembrane domain;
a cytoplasmic domain which initiates¹ a signal resulting in activation of a secondary
messenger system in the absence of a T-cell receptor, wherein said cytoplasmic domain is
selected for the group consisting of the CD3 zeta chain, the CD3 eta chain, the CD3 gamma
chain, the CD3 delta chain, the CD3 epsilon chain, the gamma chain of the F_c receptor and
tyrosine kinase, and when said chimeric protein is expressed as a membrane bound protein in
a selected mammalian host cell under conditions suitable for expression, said membrane
bound protein initiates signaling in said host cell once the extracellular domain binds to said
antigen.

59. A protein according to claim 57, wherein the cytoplasmic domain is the
gamma chain of the F_cεR I receptor.

¹ In the Amendment filed 8 March 1999, "transduces" was replaced with "initiates." Unfortunately, that claim change was not carried forward in succeeding Amendments, but is corrected herein.

APPELLANTS' BRIEF ON APPEAL

Serial No.: 08/238,405

64. A mammalian cell, comprising as a surface membrane protein the chimeric protein of claim 57.

65. The mammalian cell of claim 64, wherein said cell is a hematopoietic stem cell.

67. The mammalian cell of claim 64, which is a cytotoxic T lymphocyte.

69. The mammalian cell of claim 64 wherein said cell is not recognized as foreign in a host.